UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,001	04/21/2000	Joan C. Egrie	A-460A	1458

21069 7590 02/04/2005

AMGEN INC.
MAIL STOP 27-4-A
ONE AMGEN CENTER DRIVE
THOUSAND OAKS, CA 91320-1799

EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/559,001	EGRIE ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *49 and 50* is/are allowed.

6)☒ Claim(s) *45-48 and 51-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 18 November 2004 has been entered in full. Claims 45-78 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection to claims 45-75 under 35 U.S.C. 112, first paragraph, written description, new matter, as set forth at pages 3-4 of the previous Office Action (18 May 2004) is *withdrawn* in view of Applicant's arguments (18 November 2004).

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 45-48 and 51-78 remain rejected under 35 U.S.C. 112, first paragraph, enablement. The basis for this rejection is set forth at pages 4-7 of the previous Office Action (18 May 2004).

Applicant maintains that the claims should not be limited to those EPO analogs having the amino acid changes necessary to add a new N-linked glycosylation site at about position 114 or at positions 52, 53, 55, 86 and/or 114. Applicant argues that the specification enables far more than the specific analogs exemplified. Applicant cites Table 2 as examples of combinations of different N-linked glycosylation sites. Applicant states that it would not require undue experimentation to make additional combination of

new glycosylation sites and that the dimensional structure of EPO complexed with its receptor (Syed *et al.*) provides important information to one skilled in the art regarding location of amino acid residues in EPO which may be altered without perturbing protein structure and function. Applicant argues that the Examiner's allegation of unpredictability based upon the results of Table 2 is misleading. Applicant states that by focusing on the results of a single analog, N59, which was shown to have an *in vitro* activity of 25-75% of human EPO, the Examiner has ignored the clear disclosure of Table 2 that all but two of the analogs made and tested for *in vitro* activity retained activity equivalent to that of human EPO. Applicant asserts that the two analogs, N53 and N59 that did not exhibit full *in vitro* activity were found to retain a substantial portion (25-75%) of *in vitro* activity. Applicant states that the results in Table 2 supports Applicants' position that the claimed nucleic acid molecules are enabled and may be made without undue experimentation.

Applicant's arguments have been fully considered but not deemed persuasive. The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure because the instant claims encompass nucleic acid molecules encoding amino acid changes for glycosylation sites not taught by the instant specification. The Examiner agrees with Applicant that Table 2 teaches examples of combinations of different N-linked glycosylation sites. However, the instant claims encompass the introduction of *any number of glycosylation sites at any position in erythropoietin (EPO)*. The claims encompass the introduction of changes in unspecified positions. In addition, some of the claims fail to recite whether N-linked or O-linked

carbohydrates are attached at the additional sites. Applicant cites Table 2, however Table 2 does not teach the introduction of any number of glycosylation sites at any position in EPO. The instant claims fail to place any limit on the number of changes (substitutions, deletions, insertions and/or additions) that may be made to the EPO sequence for additional glycosylation sites. Scientific literature teaching the introduction of glycosylation sites in human EPO would not be obvious to one of skill in the art to use and modify because one skilled in the art would recognize the unpredictability of the effects of mutations on protein function and structure. Applicant cites Syed *et al.* but Syed *et al.* did not make the number of changes in EPO that is cited in the instant claims. Contrary to Applicants assertion, undue experimentation would be required.

Lastly, Applicant states that two analogs (N53 and N59) were found to retain a substantial portion (25-75%) of *in vitro* activity of rHuEPO. The specification teaches *in vitro* activity ++ as activity that is 25-75% of rHuEPO (Table 2, page 36). This means that analogs N53 and N59 could have activity as low as 25% of rHuEPO. The Examiner understands that the instant invention relates to the administration of *lower amounts* and *less frequent dosings* of EPO hyperglycosylated analogs *compared to recombinant human EPO*. Analogs N54 and N61 were not tested and only analogs N47, N50 and N53 were tested for *in vivo* activity. Applicant states that the results in Table 2 cannot be taken as evidence of unpredictability. The Examiner respectfully disagrees with Applicant. Table 2 demonstrates the unpredictability with making residue changes and the potential for altered functional properties. The specification teaches that analogs N53 and N59 could have an *in vitro* activity between 25-75% of rHuEPO. The instant

claims broadly encompass a nucleic acid molecule encoding an amino acid sequence having a N-linked glycosylation sites at any of positions 52, 53, 55, 86 and/or 114, as well as *additional glycosylation sites at other unspecified positions in SEQ ID NO:1.* A reasonable correlation must exist between the claims and an enabling disclosure set forth in the specification.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

Claims 45-48 and 51-78 remain rejected under 35 U.S.C. 112, first paragraph, written description. The basis for this rejection is set forth at pages 8-9 of the previous Office Action (19 May 2004).

Applicant argues that the specification sets forth numerous positions for additional amino acid changes in addition to those specifically exemplified. Applicant argues that the specification teaches that one may add new N-linked glycosylation sites at one or more of positions. Applicant cites page 12, lines 19-21. Applicant states that amino acid residues may be changed which are not likely to be involved in the binding of human Epo to its receptor. Applicant sites page 15, lines 31-35, and Syed *et al.* (Nature 395, 511 (1998)). Applicant argues that the specification also discloses that changes in the nucleotide sequence may result in the introduction of both N-linked and O-linked glycosylation sites. Applicant maintains that the case cited by the Examiner can be distinguished on its facts from the present application. Applicant argues that in

Fiddes, claims to all mammalian FGF's were being sought in view of a disclosure of only the amino acid sequence of bovine fibroblast growth (FGF). Applicant maintains that the extent of amino acid (and nucleic acid) sequence disclosure in the claims at issue in these cases was far less than what is presently disclosed and, in a number of instances, the structure of the claimed proteins could not be readily recognized by one skilled in the art. Applicant argues that in contrast, claim 45 recites one or more amino acid changes which provide for one or more additional glycosylation sites in residues 1-165 of SEQ ID NO:1, which represents a set of amino acid changes, which can be clearly recognized by one skilled in the art. Applicant maintains that unlike the subject matter of the cited case law, the detailed chemical structure of a number of analogs of human Epo claimed in Claim 45 can be readily envisioned.

Applicant's arguments have been fully considered and are deemed persuasive. As was stated above, the Examiner agrees with Applicant that Table 2 teaches examples of combinations of different N-linked glycosylation sites and thus the instant specification has written description support for any combination using those sites (as taught in Tables 2 and 3). The instant claim, however, allows for an unlimited number of substitutional mutations to create new glycosylation sites. A disclosure of 6-7 acceptable sites is not representative of a genus encompassing an unlimited number of individual and combination substitutions.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Allowable Subject Matter

Claims 49 and 50 are allowable.

Conclusion

Claims 45-48, 51-78 are rejected.

Claims 49 and 50 are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
2/01/05

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER